We claim:

1. A monoclonal antibody to tacrolimus that is an $IgG_1\lambda$ monoclonal antibody that has a binding affinity for tacrolimus of about 3.7×10^9 liters/mole, that cross-reacts with 13-demethyl tacrolimus, and that has less than about 8% cross-reactivity to all of the following tacrolimus metabolites: 15-demethyl tacrolimus; 31-demethyl tacrolimus; 13, 31-didemethyl tacrolimus; 15, 31-didemethyl tacrolimus; and 12-hydroxy tacrolimus and is designated 1H6.

2. A monoclonal antibody to tacrolimus that:

(a) competes with the $IgG_1\lambda$ monoclonal antibody designated 1H6 at least about 80% as effectively on a molar basis as compared with the $IgG_1\lambda$ monoclonal antibody designated 1H6 as measured by competition assays; and

(b) has less than about 10% cross-reactivity with each of 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13, 31-didemethyl tacrolimus, 15, 31-didemethyl tacrolimus, and 12-hydroxy tacrolimus.

3. The monoclonal antibody of claim 2 wherein the antibody competes at least about 90% as effectively on a molar basis as the monoclonal antibody designated 1H6 and has less than about 8% cross-reactivity with each of 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13, 31-didemethyl tacrolimus, 15, 31-didemethyl tacrolimus and 12-hydroxy tacrolimus.

4. A hybridoma producing an $IgG_1\lambda$ monoclonal antibody to tacrolimus designated 1H6 that is an $IgG_1\lambda$ monoclonal antibody that has a binding affinity for tacrolimus of about 3.7×10^9 liters/mole, that cross-reacts with 13-demethyl tacrolimus, and that has less than about 8% cross-reactivity to all of the following tacrolimus metabolites: 15-demethyl tacrolimus; 31-demethyl tacrolimus; 13, 31-didemethyl tacrolimus; 15, 31-didemethyl tacrolimus; and 12-hydroxy tacrolimus.

5. A hybridoma producing the monoclonal antibody of claim 2.

6. The monoclonal antibody of claim 2 wherein at least some of the constant regions of the antibody are replaced by human constant regions so that the monoclonal antibody is humanized.

7. The monoclonal antibody of claim 6 wherein the antibody competes at least about 90% as effectively on a molar basis as compared with the $IgG_1\lambda$ monoclonal antibody designated 1H6 and wherein the antibody has less than about 8% cross-reactivity with each of 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13, 31-didemethyl tacrolimus, 15, 31-didemethyl tacrolimus, and 12-hydroxy tacrolimus.

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8. A single-chain recombinant antibody (sFv) including therein the variable regions of an antibody to tacrolimus that:

(a) competes with the $IgG_1\lambda$ monoclonal antibody designated 1H6 at least about 80% as effectively on a molar basis as compared with the $IgG_1\lambda$ monoclonal antibody designated 1H6 as measured by competition assays; and

(b) has less than about 10% cross-reactivity with each of 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13, 31-didemethyl tacrolimus, 15, 31-didemethyl tacrolimus, and 12-hydroxy tacrolimus.

9. The monoclonal antibody of claim 8 wherein the antibody competes at least about 90% as effectively on a molar basis as the monoclonal antibody designated 1H6 and has less than about 8% cross-reactivity with each of 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13, 31-didemethyl tacrolimus, 15, 31-didemethyl tacrolimus and 12-hydroxy tacrolimus.

10. A monoclonal antibody to tacrolimus produced by fusion of antibody-producing cells from an antibody-producing mammal immunized with tacrolimus derivatized with a carboxymethyl oxime moiety at a carbon atom in the non-binding domain of tacrolimus conjugated to a high molecular weight protein with a suitable fusion partner.

11. A monoclonal antibody to tacrolimus produced by fusion of antibody-producing cells from an antibody-producing mammal immunized with tacrolimus derivatized with a carboxymethyl oxime moiety at carbon atom 22 conjugated to a high molecular weight protein with a suitable fusion partner.

12. The monoclonal antibody of claim 11 wherein the high molecular weight protein is keyhole limpet hemocyanin.

13. An antibody to tacrolimus produced by immunization of an antibody-producing mammal with tacrolimus derivatized with a carboxymethyl oxime moiety at a carbon atom in the non-binding domain of tacrolimus conjugated to a high molecular weight protein.

14. An antibody to tacrolimus produced by immunization of an antibody-producing mammal with tacrolimus derivatized with an oxime moiety at carbon atom 22 conjugated to a high molecular weight protein.

15. The antibody of claim 14 wherein the high molecular weight protein is keyhole limpet hemocyanin.

16. A conjugate comprising the antibody of claim 1 directly or indirectly conjugated to a detectable label.

17. The conjugate of claim 16 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

18. The conjugate of claim 17 wherein the label is an enzyme label.

19. A conjugate comprising the antibody of claim 2 conjugated directly or indirectly to a detectable label.

20. The conjugate of claim 19 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

21. The conjugate of claim 20 wherein the label is an enzyme label.

22. A conjugate comprising the antibody of claim 6 conjugated directly or indirectly to a detectable label.

23. The conjugate of claim 22 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

24. The conjugate of claim 23 wherein the label is an enzyme label.

25. A conjugate comprising the antibody of claim 8 conjugated directly or indirectly to a detectable label.

26. The conjugate of claim 25 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

27. The conjugate of claim 26 wherein the label is an enzyme label.

28. A conjugate comprising the antibody of claim 10 conjugated directly or indirectly to a detectable label.

29. The conjugate of claim 28 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

30. The conjugate of claim 29 wherein the label is an enzyme label.

31. A conjugate comprising the antibody of claim 11 conjugated directly or indirectly to a detectable label.

32. The conjugate of claim 31 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

33. The conjugate of claim 32 wherein the detectable label is an enzyme label.

34. A conjugate comprising the antibody of claim 13 conjugated directly or indirectly to a detectable label.

35. The conjugate of claim 34 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent, a bioluminescent label, and a particulate label.

36. The conjugate of claim 35 wherein the label is an enzyme label.

37. A conjugate comprising the antibody of claim 14 conjugated directly or indirectly to a detectable label.

38. The conjugate of claim 37 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent, a bioluminescent label, and a particulate label.

39. The conjugate of claim 38 wherein the label is an enzyme label.

40. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 1; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

41. The method of claim 40 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

42. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 2; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

43. The method of claim 42 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

44. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 6; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

45. The method of claim 44 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

46. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 8; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

47. The method of claim 46 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

48. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 10; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

49. The method of claim 48 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

50. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 1; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

51. The method of claim 50 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

~~52. A method of detecting or determining tacrolimus comprising the steps of:~~

~~(a) providing a sample suspected of containing tacrolimus;~~

~~(b) reacting the sample with:~~

(i) the antibody of claim 13; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

53. The method of claim 52 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

54. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 14; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal; and

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; or

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

55. The method of claim 54 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

56. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 1; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

57. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 2; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

58. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 6; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

59. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 8; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

60. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 10; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

61. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 11; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

62. A test kit comprising, packaged in separate containers:
(a) the antibody of claim 13; and
(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

63. A test kit comprising, packaged in separate containers:

(a) the antibody of claim 14; and

(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

64. A derivative of tacrolimus comprising tacrolimus that is derivatized with a carboxymethyl oxime moiety at a carbon atom in the non-binding domain of tacrolimus.

65. A derivative of tacrolimus comprising tacrolimus that is derivatized with a carboxymethyl oxime moiety at carbon atom 22.

66. A conjugate comprising the derivative of claim 64 conjugated to a high molecular weight protein.

67. The conjugate of claim 66 wherein the high molecular weight protein is keyhole limpet hemocyanin.

68. A conjugate comprising the derivative of claim 65 conjugated to a high molecular weight protein.

69. The conjugate of claim 68 wherein the high molecular weight protein is keyhole limpet hemocyanin.

70. A method of derivatizing tacrolimus comprising reacting tacrolimus with carboxymethoxylamine to produce a carboxymethyl oxime derivative of tacrolimus, the carboxymethyloxime moiety being located at carbon atom 22.

71. A method of producing a conjugate of tacrolimus with a high molecular weight protein comprising:

(a) reacting tacrolimus with carboxymethoxylamine to produce a carboxymethyl oxime derivative of tacrolimus, the carboxymethyl oxime moiety being located at carbon atom 22;

(b) activating the carboxymethyl oxime to produce a reactive N-hydroxysuccinimide ester; and

(c) reacting the N-hydroxysuccinimide ester with the high molecular weight protein to produce the conjugate.

72. The method of claim 71 wherein the high molecular weight protein is keyhole limpet hemocyanin.

73. A derivative of tacrolimus comprising tacrolimus substituted with a carboxymethyl oxime moiety at carbon atom 22 linked through a linker to a biotin moiety.

74. The derivative of claim 73 wherein the linker has the structure NH_2-CH_2-CH_2-NH-CO-$(CH_2)_5$-NH_2, and wherein one amine group of the linker forms an amide bond with the carboxyl group of the carboxymethyl oxime and the other amine group of the linker forms an amide bond with the carboxyl group of the biotin.

75. A method of derivatizing tacrolimus comprising:

(a) reacting tacrolimus with carboxymethoxylamine to produce a carboxymethyl oxime derivative of tacrolimus, the carboxymethyl oxime derivative being located at position 22;

(b) activating the carboxymethyl oxime to produce a reactive N-hydroxysuccinimide ester; and

(c) reacting the N-hydroxysuccinimide ester with the carboxyl group of biotin or a biotin derivative or analogue to produce a tacrolimus derivative.

76. A derivative of tacrolimus comprising tacrolimus that is derivatized with a bromoacetyl moiety at a carbon atom in the non-binding domain of tacrolimus.

77. A derivative of tacrolimus comprising tacrolimus that is derivatized with a bromoacetyl moiety at position 22.

78. A conjugate comprising the derivative of claim 76 conjugated to a protein.

79. The conjugate of claim 78 wherein the protein is a cysteine-containing mutein of glucose-6-phosphate dehydrogenase.

80. A conjugate comprising the derivative of claim 77 conjugated to a protein.

81. The conjugate of claim 80 wherein the protein is a cysteine-containing mutein of glucose-6-phosphate dehydrogenase.

82. A method of derivatizing tacrolimus comprising:

(a) reacting tacrolimus with carboxymethoxylamine to produce a carboxymethyl oxime derivative of tacrolimus, the carboxymethyl oxime derivative being located at position 22;

(b) activating the carboxymethyl oxime to produce a reactive N-hydroxysuccinimide ester; and

(c) reacting the N-hydroxysuccinimide ester with the trifluoroacetic acid salt of bromoacetyl ethylenediamine to produce a bromoacetyl derivative of tacrolimus.